REMARKS

Claims directed to model systems and methods of generating them not limited to rodents have been canceled. These are claims 19, 26, 29, 38-41, 50-53, and 62-65. Applicants believe that the specification is enabling for mammalian non-human animals in general. However, to avoid any consideration that there may have been an attempt to recapture subject matter surrendered in the issued patent, these claims have been canceled. It is believed that cancellation of these claims simplifies prosecution.

Claims 1, 11, 13, 15, 20, 22, 27 and 28, all of the remaining independent claims have been amended in an identical manner to clarify that the orthotopically transplanted intact tumor must metastasize. Support for this amendment is found in the specification of the issued patent in, for instance, column 1, lines 55-67, which explain that a deficiency of prior art models is their inability to metastasize, column 7, lines 9-13, which indicate that the clinician is allowed to identify both primary *and secondary* sites of tumor growth and throughout the specification. Further, the ability of the tumors transplanted according to the method of the invention to metastasize has been repeatedly demonstrated both by the inventors and by imitators. See, for example, Furukawa, T., *et al., Cancer Res. 53* (1991) 1204-1206 and An, Z, *et al., Clin. and Exper. Metastasis* (1999) 0:1-6. The amendment to the claims thus does not constitute new matter and emphasizes the value of the present model.

Entry of the amendment is respectfully requested. Applicants understand that this entry is discretionary after final, but believe that it is helpful in placing the claims in a position for allowance.

Status of the Application

With the cancellation of claims directed to non-rodent models or methods to prepare non-rodent models, the sole remaining issue is that of obviousness, a rejection applied to all claims over the combination of Wang in view of McLemore, and in further view of Otto. Wang and McLemore are said to teach orthotopic transplantation of tumor cells or suspensions while Otto is said to teach transplantation of histologically intact tumors, but not orthologically.

Applicants deeply appreciate the indication at the interview that the subject matter of the claims is unobvious due to the unexpected results that metastases are readily formed when a histologically intact piece of tumor tissue is surgically implanted orthotopically in comparison to the sequelae of implantation of cell suspensions where metastases are only rarely formed. The ability to form metastases greatly enhances the value of the model, as will further be discussed below. In view of the indication of allowability of the claims, applicants hope they can be forgiven for addressing on the record the issue of whether a *prima facie* case is made out by the cited documents as they believe they are obligated to do so. The understanding of the Examiner in this regard is respectfully requested.

Is There a *Prima Facie* Case?

Although the issue of whether there is or is not a *prima facie* case of obviousness is moot in light of the exceptional results obtained by applicants, applicants wish to draw the attention of the Office to the recently decided Federal Circuit cases on this point which make clear that there must be a teaching or motivation to combine the documents cited. It is not sufficient to assert that once combined the invention becomes obvious; there must be a motivation to make the combination in the first place and the Office must provide a rationale which supports this motivation. The only rationale that applicants see in the discussion of the rejection is that

> The skilled artisan would have been motivated to transplant human neoplastic tissue rather than human neoplastic cells in suspension in order to save the time and effort of generating and maintaining human cell lines *in vitro* that retain the characteristics of the original tumor.

Applicants respectfully dispute that this would be adequate motivation. There is no necessity to generate and maintain human cell lines *in vitro* that maintain the characteristics of the original tumor. Instead, it would be quite possible, as described, indeed, by McLemore to propagate xenographs "derived directly from enzymatically digested, fresh human lung tumor specimens obtained at the time of diagnostic thoracotomy and representing all four major lung cancel cell types" (see Abstract, about three-quarters of the way down). Indeed, the techniques described in the specification are actually more troublesome than those of the prior art in terms of convenience and efficiency. They are surgical techniques which require more skill than simply injecting enzymatically digested cells (or cell lines). Therefore, this asserted "convenience" cannot be the motivation to combine the documents.

Cases with respect to which applicants would request consideration include *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) which was mentioned in the previous response as well as *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999) and *In re Dance*, 48 USPQ2d 1635 (Fed. Cir. 1998). In this last instance, the decision actually went against applicants, but the criteria for motivation were consistently stated with those in *Rouffet* and *Dembiczak*. In each case, it is made clear as the Office, indeed, acknowledges that there must be a motivation to combine these documents absent the teachings of the invention.

Applicants have added the requirement for metastasis to the claims as the superiority of this model has repeatedly been demonstrated in terms of its ability to generate metastases. The McLemore paper cited by the Office discloses distant metastases only in 3% of the subjects used. On the other hand, as demonstrated by applicants' results in the paper by Furukawa, metastases

were formed in 100% of the mice with extensive primary growth. The formation of metastases is an important part of the success of the model described and claimed.

In addition to the documents cited by the Office, a paper by Shapiro, W. R., *et al., J. NCI* (1979) 62:447-453, further discussed below, describes orthotopic implantation into the brain of intact brain tumor samples when necessitated by inadequacy of the sample itself - *i.e.*, where there are insufficient cells to obtain a suspension. As discussed at the interview, applicants believe that the disclosure of Shapiro does not constitute an accidental anticipation of the claimed subject matter because brain tumors, as a generalization, do not metastasize, and clearly there was no evidence of metastasis reported by Shapiro. In addition, the disclosure of Shapiro showed that use of an intact sample as compared to cell suspensions in this particular instance was disadvantageous. Accordingly, Shapiro supplies no motivation to modify the teachings of McLemore and Wang.

Unexpected Results

The model and methods to produce it claimed herein have consistently, over the years, shown the unexpected result that the orthotopically implanted histologically intact tumors metastasize in a reliable percentage of cases, while when cell suspensions are implanted, metastases seldom occur. Enclosed herein are the following papers which present results in support of this statement.

Fu, X, *et al., Anticancer Research* (1992) 12:1395-1398 describe the results of the transplantation of histologically intact human colon cancer to the colon of immunodeficient nude and SCID mice. The data in this paper show that extensive local growth and liver metastases occur consistently even after extensive *in vivo* orthotopic passage. (See abstract, for example).

Furukawa, T., *et al., Cancer Research* (1993) 53:1204-1208, discussed briefly above, describes implantations of stomach cancer samples which are histologically intact into the stomachs of nude mice. 100% of the mice showed extensive primary growth to the regional lymph nodes, liver and lung. However, when cell suspensions were used to inject stomach cancer cells at the same site, metastases occurred only in 6.7% of the mice that had local tumor formation. These results are shown in Table 1 on page 1205.

Astoul, P., *et al., Int. J. Oncology* (1993) 3:713-718 summarizes the results of a number of papers which show the high incidence of metastases when intact tissue is transplanted. As stated in the Abstract, "by avoiding disruption of tumor integrity, we have found that orthotopic implantation of histologically intact patient specimens leads to models better reflecting the original behavior of human cancer than model constructed by orthotopic injection of cell suspensions." A number of papers are cited showing these excellent results for a number of tumors. Results are shown in Table 1 with respect to lung cancer.

An, Z., *et al., Clin. & Exp. Metastasis* (1999) 17:265-270 also showed a direct comparison of surgical orthotopic implantation of histologically intact tumor tissue and orthotopic injection of cell suspensions of renal cell carcinoma. As stated on page 267, while both models demonstrated metastases in the lung, liver and mediastimal lymph nodes, the metastatic rate for these sites was 2-3 fold higher for the implantation of intact samples as compared to implantation of cell suspensions.

Application of this model using green fluorescent protein to visualize the metastases has also been extensively reported. Exemplary publications include Yang, M., *et al., Cancer Research* (1998) 58:4217-4221. As described on page 4218, eight green fluorescent protein labeled tumors which were intact were implanted in the lung and all eight metastasize to the

collateral lung and chest wall; seven metastasized to the skeletal system. (See page 4218, right-hand column, top paragraph.)

Rashidi, B., *et al., Clin. Exp. Metastasis* (2000) 57-60 reports an additional study showing that surgical orthotopic implantation of lung tumors resulted in high percentages of metastases including to the heart, brain and mediastinal lymph nodes (see Table 1, page 60).

Finally, a series of publications on which the senior author is Shozo Baba has appeared showing that in the hands of others the surgical orthotopic implantation model induces a high degree of metastasis and thus has been used as a model system to show the efficacy of an experimental drug, TNP-470 in preventing metastasis of colon cancer.

These papers are: Konno, H., *et al., Int. J. Cancer* (1995) 61:268-271;

Tanaka, T., *et al., Cancer Research* (1995) 55:836-839;

Konno, H., *et al., Cancer* (1996) 77:1736-1740; and

Kanai, T., *et al., Int. J. Cancer* (1998) 77:933-936.

These papers straightforwardly used the surgical implantation of histologically intact cancers as a metastatic model.

Commercial Success

The immunodeficient rodent model claimed in the present application has enjoyed considerable commercial success and has generated substantial revenues for the assignee, AntiCancer, Inc., for services rendered in performing studies using this "metamouse" model. The proprietary nature of this model has been important to the assignee, and this commercial importance has been recognized by others. The counterpart patents to the present application in Europe and Japan have been opposed, in both cases by Takeda Chemical Co., because the model is of sufficient commercial importance that opposition has been considered useful. In both cases,

the opposition has failed and claims substantially equivalent to those presented here have been upheld.

Further, it has been necessary for applicants to bring suit against infringers of the Japanese counterpart, evidence of infringement was provided in the papers described above published by the Baba group.

Thus, not only are there unexpected results from using surgical orthotopic implantation of intact specimens, results not suggested in any way by any prior art document of which applicants are aware, the model itself has been a substantial commercial success.

Art Cited in the European and Japanese Oppositions

Applicants again wish to express their gratitude for the willingness of the Examiner to enter a Supplementary Information Disclosure Statement documenting the citations which form the basis of the Japanese and European oppositions alluded to previously. The opposition in Japan was settled in applicants' favor on 11 May 1999 and the opposition in Europe was decided in applicants' favor on 22 March 2001. A copy of the European opposition decision is hereby made of record and listed on a PTO 1449 form enclosed herewith.

Twelve papers were made of record in the European opposition; the first five listed (D1-D5) were the documents of record in the Japanese opposition. Documents D6-D9 of record in Europe are applicants' own publications showing unexpected results; documents D10-D12 were submitted by the opponent in order to show that on some occasions, neural system tumors may metastasize. Thus, D6-D9 have already been discussed hereinabove. Applicants wish briefly to describe the relevance of D1-D5 and D10-D12. A list of these documents is found on pages 2-3 of the decision of the EPO Opposition Division, attached to the PTO - 1449 form.

D1 was discussed briefly at the interview. In this document, the authors report that they have grown human brain tumors from six of seven patients in the brains of nude mice. Although generally cell suspensions were used, as pointed out on page 447, right-hand column at the top, if there was insufficient tissue to prepare a cell suspension the tumor was cut into small pieces and implanted surgically. Table 1 reports that when cell suspensions were used, 64% of the implantations resulted in a successful "take." However, when a fragment was used, only 24% of these tumors "took." When chemotherapy was tested in this model, only the cell suspension models were used (see page 449, "Chemotherapy Trials").

There is no report in Shapiro of any metastasis of any of the tumors and brain tumor, in general, do not metastasize; thus, the metastasis model claimed herein is not even accidentally anticipated. In terms of suggestion, if anything, Shapiro teaches away from the use of fragments since they were less successful than cell suspensions, and only used when cell suspensions were not available. Finally, as kindly acknowledged by the Examiner in the Interview Summary, the argument concerning unexpected amounts of metastases would hold for the Shapiro reference as well as for those cited.

D2: Fiddler, L. J., *Cancer & Metastasis Reviews* (1986) 5:29-49 is cumulative to already submitted and acknowledged prior art. It is a review of original papers which describe orthotopic transplantation of cell suspensions as well as non-orthotopic methods injecting cancer cells. Low metastatic rates are generally obtained. D3 and D5 are among the documents included in this review.

D3, Naito, S., *et al., Cancer Research* (1986) 46:4109-4115 has already been made of record and describes acknowledged prior art wherein cell suspensions are injected orthotopically.

D4, Kyriazis, A. P., *et al., Cancer Research* (1981) 41:3995-4000 is directed to subcutaneous transplantations. This paper is cumulative to Otto. In this regard, however, a comparison has been made by present applicants with regard to metastases produced using both the methods of D3 and of D4. These data are summarized in Fu, X., *et al., Int. J. Cancer* (1991) 49:938-939 (enclosed). While orthotopic implantation of intact tissue as described herein led to high levels of metastasis, subcutaneous implantation of intact tissue did not metastasize.

D5, Morikawa, K., *et al., Cancer Research* (1988) 48:1943-1948 is also cumulative and acknowledged prior art and describes only unsuccessful attempts to obtain metastasis when cell suspensions were implanted orthotopically as opposed to the histologically intact tissue of the invention.

Applicants wish also to comment on D10-D12 which were submitted in an attempt to dispute applicants' contention that brain tumors do not metastasize. D10, Detry, O., *et al., Transplantation* (2000) 70:244-248 is a publication more than 10 years subsequent to applicants' application date, which acknowledges the recognition that metastasis very rarely occurs from neural tissue tumors. As stated in the abstract, "patients with primary central nervous system tumor have been accepted for organ donation because these tumors very rarely spread outside the CNS". The alluded-to "recent" case reports affirm that despite isolated reports of metastasis, the rate is so low that these donors should continue to be accepted. D11 (Widjaja, A., *et al., Digestion* (2000) 61:219-222 and Lopez-Rios, F., *et al., Diagnostic Cytopathology* (2000) 23:43-45 simply represent two of these isolated reports.

Applicants again apologize for the belated submission of these documents and again express their appreciation to the Examiner for her willingness to consider them and enter them into the record.

CONCLUSION

Applicants deeply appreciate the indication that the unexpected results exhibited by the rodent model of cancer progression and metastasis presently claimed confer patentability. Accordingly, it is believed that presently pending claims 1-18, 20-25, 27-28, 30-37, 42-49 and 54-61 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530.

Respectfully submitted,

Dated: November 19, 2001 By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice amended) A nude mouse model for human neoplastic disease, wherein said mouse has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said mouse which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

11. (Amended) A method of generating a nude mouse model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of a nude mouse which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

13. (Twice amended) A nude rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

15. (Twice amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue of at least 1 mm^3 in size transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

20. (Amended) A method of generating a nude rodent model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size onto an organ of a nude rodent which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

22. (Amended) A method of generating an immunodeficient rodent model for human neoplastic disease, said method comprising:

transplanting histologically intact human neoplastic tissue of at least 1 mm^3 in size onto an organ of an immunodeficient rodent which corresponds to the human organ from which said tissue is originally obtained; and

allowing said transplanted tissue to grow and metastasize, so as to mimic progression of the neoplastic disease in the human donor.

27. (Twice amended) A nude rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.

28. (Twice amended) An immunodeficient rodent model for human neoplastic disease, wherein said rodent has histologically intact human neoplastic tissue transplanted onto an organ of said rodent which corresponds to the human organ from which said tissue is originally obtained; and

has sufficient immuno-deficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor.